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Enteric health of children in coastal Bangladesh: A cross−sectional study

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ABSTRACT

Objective: To investigate the environmental factors associated with enteric diseases among children in coastal Bangladesh.

Methods: A cross-sectional descriptive study was conducted between July 2018 and November 2018, enrolling 59 preschool children from Nabipur village in Bhola district and Paikgacha village in Khulna district. Keraniganj in Dhaka district was selected as a control village for comparison. A self-administered semi-structured questionnaire was used to collect data, including health information (height, weight, food habits, and hygiene practices), age and history of medication. Food, water and stool samples were also collected from the participants.

Results: Children in coastal zones experience an average of 6 episodes per year as compared to 3 diarrhea episodes in Dhaka. The salinity of drinking water varied significantly across the study sites (480±30 ppm in Bhola, 450±36 ppm Khulna, 180±17 ppm in Dhaka). The coastal children had higher fecal calprotectin levels (67±2.7 ng/mg and 77±12 ng/mg in Khulna and Bhola, respectively) compared to those living in Dhaka (25±1.5 ng/mg). The levels of fecal calprotectin and fecal s100A12 were both positively correlated with the salinity of drinking water in Bhola (r=0.66 for calprotectin; r=0.51 for s100A12) and Khulna (r=0.77 for calprotectin; r=0.54 for s100A12).

Conclusions: The study revealed a positive correlation between the salinity levels in drinking water and the elevated levels of fecal calprotectin and fecal s100A12 in children living in coastal villages of Khulna and Bhola in Bangladesh, whereas no such association was found among children living in central Bangladeshi locality of Keraniganj, Dhaka.

KEYWORDS: Preschool children; Calprotectin; s100A12; Bangladesh

1. Introduction

More than 4.5 million children living in the coastal Bangladesh are vulnerable to the effects of natural disasters, changes in livelihood, and global climate change[1]. The international research teams have increased the scrutiny of the environment and climate of the coastal belt of Bangladesh in the past decades[2,3].

In this study, we hypothesized that diarrheal episodes might be

Significance

Salt has been identified as a cause of mucosal inflammation and gut microbiome dysbiosis in rodent models. This study reports that the salinity of drinking water from coastal villages in Bangladesh is correlated with two distinct markers of mucosal immunity (fecal calprotectin and s100A12) in preschool children, providing a basic explanation for the increased prevalence of enteric diseases among children in the Bangladeshi coastal population.

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related to environmental parameters in rural coastal Bangladesh. We quantified two fecal biomarkers (Calprotectin and s100A12) in the digestive system to assess the mucosal health of the participants. Calprotectin is a 36.5 kDa protein belonging to the s100 family, which is secreted from mucosal neutrophils[4,5]. A study reported a calprotectin level of 53-119 ng/mg in stool among malnourished Asian children[5,6]. The bacteriostatic and mycostatic activity of calprotectin varies significantly across populations and age-groups[7,8]. A fecal calprotectin level beyond 50 ng/mg, along with diarrhea, stomach ache and indigestion are indicative of inflammation[8, 9].

Fecal s100A12 is predominantly secreted by neutrophil and monocytes, acting as a chemotactic molecule pattern protein[10,11]. The cut-off value of s100A12 in stool is 10ng/mL for healthy children, while is 100-1100 ng/mL for symptomatic cases of inflammatory bowel disease[4]. Elevated levels of fecal calprotectin and s100A12 indicate inflammation in the intestine[11].

In recent times, several biological processes have emerged as key factors in maintaining mucosal health. Nutrition, immunity, the eubiosis of gut microbiome and social well-being are reported to be the major contributors to mucosal health in preschool children[12–16].

2. Materials and methods

2.1. Ethical approval

The enrollment of child participants was conducted in adherence with guidelines from Bangladesh Medical Research Council for Research with Human Subjects. The concept and research methods of this study were reviewed and approved by the Director of Research, Jagannath University, Dhaka (Project-JnU/Research/1743/2018-19) on January 21, 2018.

2.2. Study design

A cross-sectional descriptive study was conducted in two rural coastal areas of Bangladesh, namely Nabipur village in Bhola district and Paikgacha village in Khulna district between July 2018 and November 2018. Bhola is an island district located in Southern part of Bangladesh. Ihe area is about 3 403 square kilometers with 9 million inhabitants. The majority of people in the area are farmers and fishermen, living a rural lifestyle with limited municipal infrastructure developments. Deep tubewells are the main source of drinking water and farmers markets are the main source of food. The monthly income ranges from 14 000 to 20 000 Bangladeshi Taka (BDT), with an average family size of 8-10 people (joint families).

Khulna is a district in Southern Bangladesh covering an area of about 4 394 square kilometres with Sunderbans mangrove forests and Bay of Bengal to its South. The sampling location Paikgacha village lacks municipal infrastructure. Deep tubewells and ponds are the main sources of drinking water. Fecal-oral route is a common way of disease transmission. Most inhabitants are agrarians, and the majority have secondary technical education with a monthly income of 16 000 BDT and the average family size is around 5 to 6 people (2 adults and 3 children)[17].

This study was designed to collect basic health information and to assay two common biomarkers of enteric inflammation among pre-school children (age 3-5 years). One control population (Mandipara, Keraniganj) with similar socio-economic conditions but lower salinity in soil and water was chosen as the control population. Keraniganj is a municipal sub-urban community with heavily industrialized zones. The inhabitants live in slums with piped supply water and grocery stores[18]. They get their grocery and other amenities from make-shift temporary markets (Bazars). Most people are educated up to the higher secondary level with an income of 20 000-25 000 BDT per month with an average family size of about 5 to 6 people (typically 3 adults and 2 children).

A self-administered semi-structured questionnaire was used to collect basic health information from the household adopting convenient sampling technique (sample questionnaire in supplementary material). We reached the households and the targeted populations, including preschool children and localities through local health workers, filled out the questionnaires from primary caregivers of the child to obtain the basic health data. We screened the health data to select children who are apparently healthy (without congenital, developmental difficulties, no history of serious illness in past 12 months). We contacted the guardians of the children to obtain their consent for the collection of stool samples. Children who met these criteria and whose guardians provided informed written consent for the collection of stool samples were enrolled in the study. Children with chronic

diseases (congenital defect, asthma, developmental delay), intake of antibiotics and immune-suppressor during the study period, underweight/ overweight, or whose guardians abstained from providing consent were excluded from this study. However, children who had consumed antibiotics within the last 6 months prior to the commencement of the study were included in sample collection.

2.2. Field sampling

The sampling locations for this study are illustrated in Figure 1. Nabipur village, located 116 km from Dhaka city, is connected to the site of research (Jagannath University, Dhaka) by waterways through a 6-hour journey by water vessels. Paikgacha is 228 km away from the site of research and a journey by road takes 6.5-7.0 hours via the Dhaka-Khulna highway. The Mandail neighborhood in Keraniganj is 17 km away from the site of research, taking a 30 minute journey by road via the 2nd Buriganga bridge.

At least 5 grams of solid stool specimen were collected from each child under study in a sterile, wide-neck, screw-cap container and transported to the laboratory at ice-cold temperature within 12 hours of collection. Each specimen was collected from apparently children between 2-5 years of age, labeled with clear ID, date and time of collection. Specimens accompanied with incomplete questionnaire, improper quantities and labeling defects, extended period of delay before reaching laboratory were discarded. Fourteen fecal specimens were collected from a community located in Keraniganj, 21 in Khulna and 24 in Bhola.

Twenty-five grams of rice and curry samples were collected aseptically in triplicate from each household under study from the three communities. Furthermore, 100 milliliters of drinking water samples were also collected in the triplicate from each household under study. The stool samples were mixed into a buffer and frozen for analysis at a later date.

2.3. Analysis of sodium in food and drinking water

Portable conductivity meter (Xylem, Korea) was used to measure the NaCl concentration in food and water samples following the manufacturer's instructions. Solid samples were homogenized to liberate the sodium ion in deionized (DI) water (e.g. a 5 grams of food was diluted in 95 mL Deionized water) and were measured immediately using the probe.

2.4. Quantification of fecal calprotectin with immunochromatography

A total of ten mg of the frozen stool sample was diluted in 10 mL of collection buffer (Calprotectin Immunochromatography kit, Veda Lab, France), incubated at room temperature for 30 minutes, followed by 20 µl of this preparation was applied on the introduction port of the device from the commercial kit. The presence of a purple/blue band indicates diffusion of the correct amount of sample in the device and the presence of red band indicates presence of more than 25 µg/mL of Calprotectin in stool[12]. All samples were



Figure 1. Locations of the target communities and control community in Bangladesh.

scanned using a Veda Lab Easy-Reader Optical Densitometer, which measures the actual concentration of Calprotectin in μg/mL above the cut-off value of fecal calprotectin level (≤25 μg/mL).

2.5. Quantification of fecal s100A12 with semi–quantitative ELISA

One milligram of stool sample was diluted in the dilution buffer from Circulex s100A12/En-RAGE ELISA kit (MBL Corporation, USA), vortexed and added to pre-coated ELISA plates from the kit, then was incubated for 30 minutes at 37 ℃. The plate was washed twice with wash buffer from the kit, incubated with 50 μL of secondary Ig for 30 min at 37 ℃, washed twice with wash buffer before adding to the chromogen. The optical density of the samples was measured after 10 min of addition of the chromogen for accurate measurement with Ensight microplate reader (Parkin Elmer, NJ, USA). This kit measures optical densities proportionate to s100A12 concentrations quantitatively from biological samples and determines the actual concentration of s100A12 (ng/mL) using CurveFit ELISA plot analyzer software (v1.5), with reference to the standards provided in the kit[19].

2.6. Statistical analysis

Two biomarkers of mucosal inflammation (fecal calprotectin and fecal s100A12) were expressed as functions of the amount of NaCl in drinking water. The mean values of NaCl and fecal calprotectin were used to calculate the Pearson's correlation coefficient between the two parameters, where NaCl concentration is the independent variable (x) and fecal calprotectin is the dependent variable (y) according to the following equation:

$$r = \frac{n(\Sigma xy) - (\Sigma x)(\Sigma y)}{\sqrt{[\, n\Sigma x^2 - (\Sigma x)^2 \,][\, n\Sigma y^2 - (\Sigma y)^2 \,]}}$$

Likewise, the mean values of NaCl and fecal s100A12 (ng/gm) were calculated to see if the two parameters were statistically correlated with the same equation, where NaCl concentration is the independent variable (x) and fecal s100A12 (ng/gm) is the dependent variable (y). All the statistical analyses were done in MS Excel 2020.

3. Results

This project investigated intestinal inflammation in children from coastal villages of Bangladesh. Figure 1 shows the locations of the sampling sites in Bangladesh. Table 1 and Table 2 summarized the basic personal health data of the participants. Among the 59 participants, there were 14 from Dhaka (43% male and 57% female), 24 from Bhola (50% male and 50% female), and 21 from Khulna (38% male and 62% female). The participants from Khulna had lower body max index (BMI) compared to those from Dhaka and Bhola. The BMI of participants from Dhaka, Bhola and Khulna was above the normal range (15.56±0.079 for boys at 3 years and 15.19±0.087 for boys at 5 years, 15.40±0.085 for girls of 3 years and 15.27±0.097 for girls at 5 years of age)[20]. The Dhaka population had high rates of Caesarean surgery compared to coastal communities (42.9% in Dhaka as compared to 12.5% and 14.3% in Bhola and Khulna, respectively). This study showed that 10.5% children in Dhaka, 5% in Bhola and 18% in Khulna didn't receive the mandatory nationwide childhood vaccination. In addition, 15%, 10% and 16% participants from Dhaka, Bhola and Khulna consumed antibiotics, respectively. Children from Dhaka suffered on average from 3 episodes of enteric diseases per year (diarrhoea, dysentery, worms, and cramps), whereas children from Bhola and Khulna suffered on average from 6 episodes of enteric diseases per year. The onset of major neurologic responses at the month of age. The significant difference occurs in the age which children begin to walk, run, read and write between Dhaka, Bhola and Khulna (P<0.05).

Table 3 shows the basic information of the participants, including daily water intake in litres, frequency of handwashing and utensil washing per day, as well as the frequency of weekly shower and laundry, educational status of parents or primary caregiver. The laundry habits in Dhaka community was significantly different from those in Khulna (P<0.05) and Bhola (P=0.05) according to Student's t-test. There was no significant difference observed among the level of education of the parents or primary caregivers.

The NaCl in the food and water of the households enrolled in the study was quantified, as shown in Table 4. The mean concentration of NaCl were 480±11 ppm in raw food, 700±14.3 ppm in cooked food and 180±17 ppm in drinking water samples collected from Dhaka. In Bhola, the mean concentrations of NaCl in samples were 500±21 ppm in raw food, 840±35 ppm in cooked food and 480± 30 ppm in drinking water. In Khulna, the mean concentration of NaCl was 560±23 ppm in raw food, 680±28 ppm in cooked food and 450±36 ppm in drinking water. While the raw food contained a comparable amount of salinity, there was a difference in the salinity between cooked food and drinking water of central Keraniganj, Dhaka, as well as coastal Bhola and Khulna. There was a significant difference in the salinity levels of cooked food between the control group and both coastal villages (P<0.05), while there was also a

significant difference in the salinity levels of drinking water among Dhaka, Bhola, and Khulna (P<0.05).

The quantification of fecal calprotectin is presented in Figure 2. The average amount of fecal calprotectin in children was 25±1.5 ng/mg, 77±12.8 ng/mg and 67±16 ng/mg in stool samples from Dhaka, Bhola and Khulna, respectively. The amount of NaCl in the drinking water of Bhola and Khulna was positively correlated with the level of fecal calprotectin from the samples of Bhola and Khulna, with correlation coefficient of 0.66 and 0.77 respectively. In Dhaka, the NaCl concentration was negatively correlated with the level of fecal calprotectin.

Figure 3 reveals the correlation between the fecal s100A12 levels and amount of NaCl in drinking water. The average values for fecal s100A12 among children from Dhaka, Bhola and Khulna were 105.07±6.80 ng/mL, 139.55±24 ng/mL, 113.3±13.25 ng/mL, respectively. The salinity of drinking water in Bhola was correlated with the OD value of fecal s100A12, with a correlation coefficient of 0.51 (Figure 3B). The correlation coefficients for the samples from Dhaka and Khulna were 0.32 and 0.54 respectively.

Table 1. Basic health information from communities.

Variables	Dhaka	Bhola	Khulna
Sex [*n* (%)]			
Male	6 (43)	12 (50)	8 (38)
Female	8 (57)	12 (50)	13 (62)
Average body-mass index	20.1	20.2	19.0
Mode of childbirth [*n* (%)]			
Natural	7 (50.0)	20 (83.3)	17 (81.0)
C-section	6 (42.9)	3 (12.5)	3 (14.3)
Others	1 (7.1)	1 (4.2)	13 (4.8)
Mean birthweight (Kg)	2.8	2.5	2.6
Vaccination status (%)			
Complete	89.5	95.0	72.0
Incomplete	10.5	5.0	18.0

Table 2. Current health conditions of participants

Variables	Dhaka	Bhola	Khulna
Antibiotic consumption in last 12 months	15	10	16
Episodes of enteric diseases per year	3.2	6.0	6.0
Developmental milestones (month)			
Crawling	8	6	8
Sitting	5	6	6
Talking	13	18	15
Walking	12	18	20
Running	18	22	22
Response	6	6	5
Reading/Writing	36	46	50

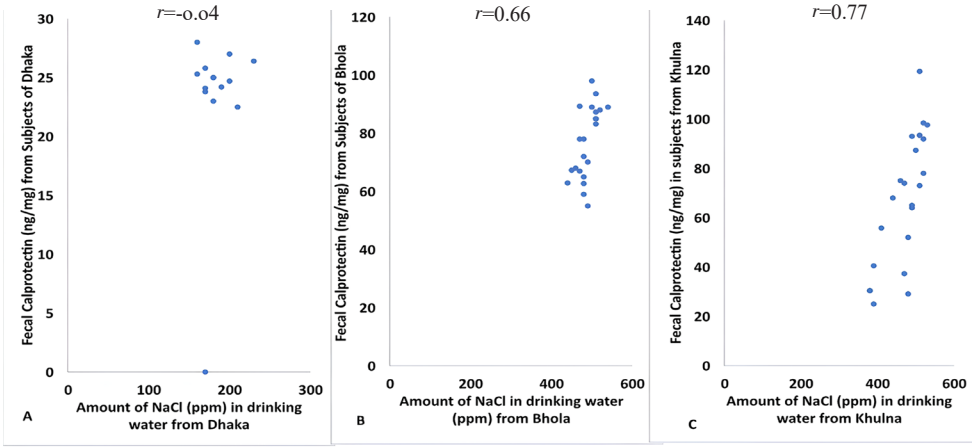

Figure 2. Correlation of salinity in drinking water and fecal calprotectin (ng/mg) levels.

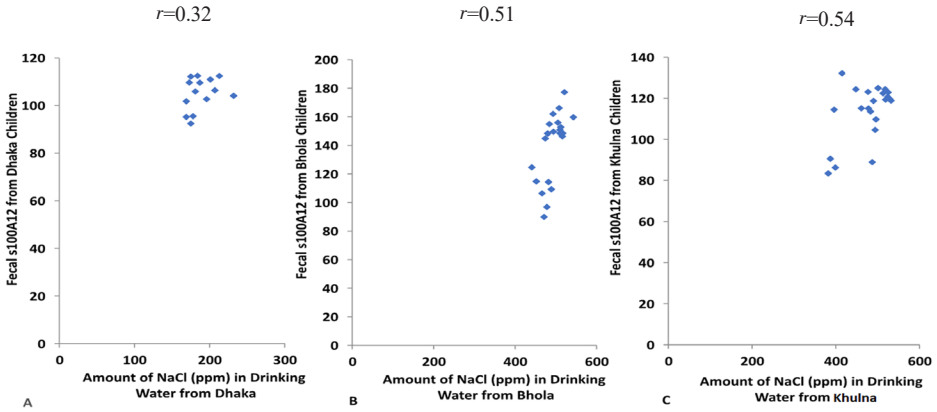

Figure 3. Correlation of salinity in drinking water and fecal s100A12 (ng/ml) levels.

Table 3. Habits and social factors related to health.

Variables	Dhaka	Bhola	Khulna
Daily water intake (in L)	2.3	1.7	1.5
Hygiene Habits (Frequency)			
Daily handwashing	7	8	10
Daily Utensil washing	3	2	3
Weekly shower	7	7	7
Weekly laundry	6	4	3
Educational qualification of primary caregiver [*n* (%)]			
No education	2 (14.3)	5 (20.8)	5 (23.8)
Primary	4 (28.6)	7 (29.2)	4 (19.1)
Secondary	3 (21.4)	6 (25.0)	5 (23.8)
Post-secondary	5 (36.7)	6 (25.0)	7 (33.3)

Table 4. Salinity of food and water from the study sites (in ppm).

Sites	Raw food	Cooked food	Drinking water
Dhaka	480+11	700+14.3	180+17
Bhola	500+21	840+35	480+30
Khulna	560+23	680+28	450+36

4. Discussion

This study was based on the hypothesis that environmental factors in rural coastal areas of Bangladesh may contribute to an increased episodes of enteric diseases. The study has several primary outcomes. Drinking water from tube-wells in the coastal areas has salinity levels ranging from 450±36 ppm to 480±30 ppm, which exceeds the WHO defined-range for salinity in drinking water (100 ppm)[21]. The Department of Public Health Engineering (DPHE), Government of Bangladesh, has a set a standard value for salinity of 200 ppm in drinking water supplied by Water Supply and Sewage Authorities[22]. The salinity levels in drinking water from the coasts are high, even compared to Bangladesh's standards.

Preschool children from Nabipur village in Bhola district of Bangladesh have high levels of fecal calprotectin and s100A12, both exceeding the values of healthy pre-school children[23,24]. The fecal biomarkers, calprotectin and s100A12, are statistically correlated to the concentration of NaCl (ppm) in drinking water. The correlation coefficient between the level of salinity of drinking water and fecal calprotectin and fecal s100A12 for the children from Khulna is higher than the range expected from healthy children, indicating that high salinity of water may potentially trigger pro-inflammatory conditions in pre-school children, although the level is lower than the clinical range for development of full-blown chronic inflammatory conditions such as Inflammatory Bowel Disease (400 ng/mg)[8,25].

Children from Dhaka revealed the salinity of drinking water from municipal supply was 180±17 ppm, which is higher than the standard set by WHO for drinking water salinity but within the range of national standard set by DPHE. Fecal calprotectin and s100A12 levels were below or close to the range of calprotectin and s100A12 in healthy children (25±1.5 ng/mg and 105.07±6.80 ng/mL), and there was no correlation between the salinity of drinking water and fecal biomarkers in the children from control community[26].

The primary outcomes could indicate the emergence of a health crisis. High salt intake may lead to kidney damage, high blood pressure, autoimmune conditions, gynaecological conditions and miscarriage[27, 28, 29]. Recently, Wilck *et al*. (2019) found an unforeseen role due to the consumption of high salt with fat, which causes the dysbiosis of gut microbiome and rise in pro-inflammatory markers in mice and men[30]. Several studies have reported similar findings and have shown that the eubiosis of the gut microbiome is an integral part of overall well-being of humans by modulating brain, immunity, cardiovascular health and nutrition[31]. A comprehensive action plan and formulation of policy require an in-depth investigation of molecular epidemiology of the disturbances caused by salinity in young children, as well as the availability of alternate sources of fresh, safe drinking water for marginalized communities.

The limitations of this study include the enrollment of too few participants from only three communities, may result in sampling bias. Furthermore, the immune assay (rapid chromatography and quantitative ELISA) were conducted using thawed samples and there is a lack of analytical data on nutrition, hygiene, basic medical parameters of health.

5. Conclusions

This study shows that dysbiosis of the gut microbiome is associated with high salt intake. Global efforts are underway to mitigate the impact of climate change on human health, including the development of salt-tolerant foods and sustainable desalination of ocean water. An extended study with more participants would help fill the knowledge gaps and facilitate the development of a meaningful action plan for sustainable management of intestinal health in affected children.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

Towhid ST devised the project, acquired and managed the grant, Hasan A collected the samples and conducted the experiments, Hassan Z wrote and revised the manuscript, Islam MA supervised the project and checked the results.

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